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THE EFFECT OF CHLORTETRACYCLINE AND SULFAMETHAZINE IN STARTER RATIONS ON THE SELECTION OF RESISTANT ESCHERICHIA COLI

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Objective:

The use of antimicrobial drugs at subtherapeutic levels as growth promotants is common practice nowadays. It has been suggested that such practice is liable to select strains resistant to antibiotics and that this may jeopardize the treatment of infectious diseases in both human and animal populations. The objective of this study was to monitor possible short and long term changes in the antimicrobial susceptibility patterns of E. coli isolated from calves fed chlortetracycline (CTC) and sulfamethazine (SMZ) at subtherapeutic levels in their starter rations.

The sensitivities of E. coli strains to 13 different antimicrobial drugs were checked. These strains were obtained at different times (premedications in the feed; i.e. day 0; days 3; 15; 28; and 98) from 4 groups of animals (Groups A to D):

A) Animals fed CTC/SMZ for 28 days, never treated therapeutically.
B) Animals fed CTC/SMZ for 28 days, and which at some stage of such period were treated therapeutically (with OTC) for respiratory disease.
C) Control animals not fed antimicrobials, never treated therapeutically.
D) Animals not fed CTC/SMZ, but treated at some stage therapeutically as for Group B.

Results and Discussion:

Strains of E. coli from the animals fed CTC/SMZ had a remarkably higher percentage of resistance; this was more obvious in the therapeutically treated groups (up to 73% of strains from Group B at days 15 and 28 versus 20% and 0% in corresponding Group D in similar days). These strains were resistant to CTC and/or SMZ as well as to other unrelated antimicrobials.

The percentage resistance dropped markedly by day 98 (i.e. 70 days after the withdraval of CTC/SMZ from feed), however, at that time groups from animals fed antimicrobials still had remarkably higher percentage resistances than their counterparts (10% Group A versus 1.6% Group C; and 13.3% Group B versus 0% Group D).

These results indicate that:
1) The use of CTC/SMZ in the rations selected resistant strains of E. coli.
2) This selective effect was greatly enhanced by the therapeutic use of CTC in those animals fed CTC/SMZ.
3) Resistance to antimicrobial drugs unrelated to the ones used in the feed, was observed concomitantly, therefore therapeutic agents other than those used as growth promotants could reinforce the selection of resistant strains in field conditions.

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(continued)

4) The selection of multiresistant strains suggests that the process is plasmid-mediated and therefore there is a potential for transmission to bacteria from other animals or man.

Further surveys, monitoring antimicrobial resistance patterns in controlled field situations, would be very useful in following the dynamics of spread of resistance in the flora of animals and the possible impact of this on the therapy of infectious diseases of man and animals.

SUMMARY

Drugs are used as additives in livestock feeds for growth promotion and the prevention and treatment of infectious disease. Feed medication with subtherapeutic levels of chlortetracycline and sulfamethazine (Aureo S-700) in the starter ration of newly arrived calves to reduce losses from pneumonia is common-place in many feedlots. Most published reports of experimental trials indicate improved growth rate and feed efficiency while the feed medication is present; usually the first twenty-eight days on feed. Few trials, however, evaluate growth performance once the feed medication is withdrawn. Our field trial results fail to show any benefit in average daily gain with Aureo S-700 beyond the first twenty-eight days on feed. Compensatory growth most likely occurred in control calves, to reduce any initial benefit seen in average daily gain in the medicated calves.

To date there is insufficient evidence to indicate that the use of chlortetracycline and/or sulfamethazine in the feed of feedlot cattle under stress will consistently reduce the occurrence of pneumonia. The results from our study fail to show any reduction in treatment rate for respiratory disease by medicating calves with Aureo S-700 for the first twenty-eight days post-arrival. Laboratory results also suggest that effective concentrations of the drug cannot be achieved in the lung unless very large doses of tetracycline are fed. Large doses of tetracycline given orally are reported to cause digestive upsets and their use is not recommended in cattle feed.

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SUMMARY

(continued)

Consumer concern has increased lately over the issue of antimicrobials in the feed. There is the potential that drug resistant bacteria could develop and be transferred from cattle to man and cause intractable disease. Increased drug resistance in the cattle population may also reduce treatment response in sick cattle. Particular concern has been expressed in regards to the use of subtherapeutic levels of antibiotics in the feed. Microbiology results from this trial (Dr. Chirino) show increased drug resistance in fecal bacteria of calves fed Aureo S-700.

Based on the lack of any benefits in performance of medicated calves, and the potential hazards related to drug resistance, the use of Aureo S-700 in feeder calves for the prevention of respiratory disease cannot be routinely recommended.

CONCLUSIONS AND IMPACT:

Low levels of antimicrobials have been used in the feed of cattle in an attempt to treat, control, or prevent respiratory disease. Feed antimicrobials have also been used as growth promotants. Numerous trials have been performed over the years, but results on the efficacy of feed medication are controversial. Frequently the trials are performed in a controlled experimental setting. Whether these results can be applied to the commercial situation is unknown. Few trials measure weight gain beyond the first twenty-eight days on feed. Our results show a benefit in average daily gain with feed medication in the first twenty-eight days on feed, but when the calves are monitored over the following six months this benefit disappears. Therefore, compensatory gain most likely occurs in the unmedicated cattle.

The efficacy of feed antimicrobials in reducing the treatment rate of respiratory disease is poorly documented. Generally, the incidence of disease is too low to show any effects of treatment. The treatment rate was 8% for calves fed antimicrobials and 12% for the unmedicated controls. Statistically, there was no benefit in using CTC/SMZ in the feed for reducing the incidence of respiratory disease.

Our trial results show similar isolation rates of Pasteurallae among treated and untreated calves. Antimicrobial sensitivity patterns in nasal isolates also were unaffected by treatment. These results suggest that the level of drug used was too low to reach systemic blood levels and be ineffective in the respiratory tract. Minimum inhibitory concentration (MIC) levels were less than or equal to 0.5 mcg/ml for tetracycline. Published data by Hjerpe suggests that MIC levels of 1 - 2 mcg/ml for tetracycline are

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CONCLUSIONS AND IMPACT:

(continued)

required for inhibitory antimicrobial concentrations. Doses of 40 mg/lb body weight per day of tetracycline are required to reach this MIC level, much higher than recommended levels mixed in the feed. Adverse effects on ruminal flora preclude the use of large doses of tetracycline by the oral route for management of acute respiratory disease.

Microbiology results from an independent study (Dr. Chirino, see attached abstract) show an increased resistance in fecal E. coli isolates in medicated calves. The potential transmission of antimicrobial resistance from bacteria of cattle to the normal flora of humankind is of great concern in therapy of infectious diseases of both man and animals. The development of resistance in cattle fed antimicrobials in the feed should continue to be investigated.

Based on the lack of prophylactic benefits and the potential harmful effects of increased drug resistance, there is little justification for the use of low levels of CTC/SMZ in the feed for the control of bovine respiratory disease.

THE VALUE OF CHLORTETRACYCLINE AND SULFAMETHAZINE IN STARTER RATIONS ON HEALTH AND PERFORMANCE OF FEEDER CALVES

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INTRODUCTION:

Undifferentiated bovine respiratory disease (UBRD) is the most common cause of sickness and mortality in the feedlot (1). Epidemic curves show the highest incidence of UBRD occurs within the first two weeks after arrival in a feedlot (1). Mass medication of newly arrived calves with antimicrobials in the feed, water, or by injection to control the incidence of UBRD has met with variable success (2-10). Feed medication with subtherapeutic levels of antimicrobials to newly arrived calves is common-place in many feedlots, yet their efficacy in regards to improved weight gain and reduced morbidity is largely unsubstantiated (2,4,6,7). The cost of such feed medication is relatively low, therefore, even if the benefits are questionable, many feedlot operators have elected to continue with their use in the hope that they will improve health and performance in stressed feeder calves. With the increasing consumer concern regarding residues in beef (11-16), it is essential, however, that the benefits and rationale for all antimicrobial use be thoroughly evaluated.

In this study, we attempted to determine the efficacy of prophylactic subtherapeutic feed levels of chlortetracycline (CTC) and sulfamethazine (SMZ) in reducing the treatment rate of UBRD, and in improving the weight gain of newly arrived calves. Antimicrobial sensitivity patterns of nasal isolates of Pasteurella were monitored throughout feed medication.

MATERIALS AND METHODS:

Animals:

Five hundred Charolais cross steer calves, between 209 and 351 kg, were purchased from four different Saskatchewan auction markets on October 21, 23, 24, and 28, 1987. Immediately upon arrival at the University of Saskatchewan feedlot each calf was individually identified, weighed, and processed. Each calf was vaccinated against infectious bovine rhinotracheitis, clostridial diseases, and Haemophilus somnus infection, treated for parasites (Ivomec), and castrated, if required. The calves were placed in 13 pens, each with a capacity of about 35 head. Free-choice grass hay was provided.

The calves were checked daily and those judged to be sick by the pen-checkers were removed from the pen ("1st pull") to a hospital facility for evaluation. A diagnosis of UBRD was made based on depression, increased respiratory rate, lack of rumen fill, and a rectal temperature greater than 40 degrees C. Sick calves were identified, treated by a standard treatment regime, and returned to their home pen. Sick calves were treated until a clinical response and normal rectal temperature (<40 degrees C) were evident for two consecutive days.

On November 3, 1987 calves were sorted by weight. Two hundred and eighty-one calves, weighing from 270 to 351 kg, were selected to remain at the University of Saskatchewan feedlot for

a nutritional trial. The remaining two hundred and nineteen calves, weighing from 209 to 270 kg, were trucked 270 km from Saskatoon to Termuende Ranch at Lanigan, to be utilized in the Aureo S-700 trial.

Randomization:

Two hundred and nineteen calves, which arrived at Termuende Ranch on November 4, 1987 were systematically randomized within purchase group into two feeding pens. By the flip of a coin, one pen became the medication feed pen and the other pen became the control feed pen. Pen 1 and pen 2 were similar in design and size, except for a shelter in pen 2. One hundred and nine calves were placed in pen 1, the medicated pen, and one hundred and ten calves were place in pen 2, the control pen.

Medication:

Chlortetracycline (CTC) and sulfamethazine (SMZ) [Aureo S-700 G, Cyanamid] were mixed into the medicated barley supplement at the University of Saskatchewan feedmill. Aromostat (Prairie Micro-tech), a flavoring agent, was added to the medicated and unmedicated barley supplement, to mask the flavor, color, and smell of the Aureo S-700 present in supplement 1. The medicated and unmedicated supplement were bagged, labelled

supplement 1 and 2 respectively, and shipped to Termuende Ranch. The feed-men and pen-checkers were unaware of the medication status of each pen (blind trial).

Aureo S-700 was added to barley supplement 1 to provide CTC and SMZ at a rate of 700 mg of each per head per day for the first seven days on feed. The medication was reduced to provide CTC and SMZ at a rate of 350 mg of each per head per day for the next twenty-one days on feed. December 2, 1987 was the final day of feed medication with Aureo S-700.

Feeding Program:

Calves in pen 1 and pen 2 were fed identical rations except for the Aureo S-700 in the ration of pen 1. Aureo S-700 was removed from the ration of pen 1 on December 3, 1987. The composition of the rations fed from November 4, 1987 until April 19, 1988 is shown in Table 1.

TABLE 1. COMPOSITION OF RATIONS FOR CALVES IN PEN 1 AND PEN 2 AT TERMUENDE RANCH ON THE AUREO S-700 FEED TRIAL

	RATIONS:+			
INGREDIENT	Nov 4-Dec 2	Dec 3-15	Dec 15-Jan 1	Jan 1-Apr 19
barley straw	ad lib	ad lib	ad lib	ad lib
barley silage (/head/day)	9 lbs	9 lbs	20 lbs	20 lbs
alfalfa grass hay (/head/day)	3 lbs	3 lbs	3 lbs	3 lbs
* barley supplement (/head/day)	1 lb	-	-	3 lbs
vitamin/ mineral supplement	ad lib	ad lib	ad lib	ad lib

+ rations were limited to restrict weight gain to 0.45 kg/head/day so that calves could be used in a nutrition trial in the spring

* Aureo S-700 added to barley supplement 1. Removed December 3, 1987

Measurements:

The following measurements were taken on arrival (November 4, 1987), November 2, November 16, and December 2, 1987. Each calf was weighed, and a rectal temperature measured. When the rectal temperature was greater than 40 degrees C the calf was identified on a health record and treated by a standard treatment regime. Deep nasal swabs were collected from each calf, placed in Amies transport medium, and sent to the Diagnostic Bacteriology Laboratory at the Western College of Veterinary Medicine (WCVM) for bacterial culture. The Kirby-Bauer antibiotic sensitivity test was performed on nasal swabs from calves with no prior treatment for UBRD. Blood samples in heparin were collected on each calf for analysis of CTC and SMZ concentrations in plasma. Fecal samples were collected for a study by the Microbiology Department at WCVM. Weights were measured every 28 days until April 19, 1988.

Calves were checked twice daily for sickness. If signs of depression, loss of rumen fill, and increased respiratory rate were present, in addition to a rectal temperature greater than 40 degrees C, a diagnosis of UBRD was made. Sick calves were treated by a standard treatment regime and returned home each day of therapy. Oxytetracycline LP was the first choice antimicrobial, used at a rate of 5 cc per 45 kg body weight, intramuscular, daily. If no reduction in temperature was apparent 48 hours after initiation of therapy, Trimethoprim/sulfadoxine was used at a rate of 3 cc per 45 kg

body weight, intramuscular, daily. Treatment was continued until the rectal temperature was below 40 degrees C for two consecutive days and clinical response was apparent.

All mortalities were necropsied by the Pathology Department of WCVM.

Statistical Analysis:

Records were maintained on disease, treatment rate, drugs utilized, mortality, and weight. Chi-square analysis was used to compare treatment data in the medicated and control pen. Mean weight and average daily gain in calves in pen 1 and pen 2 were compared utilizing the Z test for nonparametric data.

RESULTS:

A summary of the treatment data for the two hundred and nineteen calves chosen to be utilized in the Aureo S-700 trial is given in Table 2A. Twenty-seven percent of the calves were treated for UBRD at the University feedlot, from October 21 to November 3, 1987. Treatment rate for UBRD peaked on the third day after arrival (Figure 1). The relapse rate in these calves was high, at 47%. A further eighteen percent were treated on arrival at Termuende Ranch, November 4, 1987. Twenty-four percent of these calves subsequently relapsed with UBRD.

As a result of the high incidence of UBRD in the calves prior to initiation of the trial, only 137 calves were left that were apparently healthy and could be utilized as study subjects. A summary of treatment data for these calves is given in Table 2B. From Figure 2, it appears that the pattern of respiratory disease among the control and the medicated group is similar, yet the incidence of treatment for UBRD appears higher in the control group. When the relationship between Aureo S-700 medication and treatment for UBRD is analyzed, however, there is no statistical difference in treatment rate among the two groups (Table 3 & 4).

Even though only 137 calves were suitable subjects for the Aureo S-700 trial, the entire 219 calves initially selected for study were randomized within the two feed pens. Relapse rate in sixty calves initially treated at the University of Saskatchewan feedlot was not statistically different among the medicated and control group (Table 5).

Drug response rate in sick calves in the medicated pen was 81% versus 93% in the control pen (Table 2B). This difference, however, was not statistically significant.

There was no statistical difference in the final mean average weight of calves among the medicated and control group (Table 6). Mean average daily gain in calves, calculated every 28 days on feed, was variable among the two groups (Table 7). Examination of average daily gain over the entire feeding period (172 days) revealed no statistical difference among the medicated group (0.52 kg/day), and the control group (0.51 kg/day).

P. haemolytica isolation rate from nasal swabs of calves that had no prior treatment for UBRD, regardless of feed medication, declined significantly (Chi-square, P<.01) from 40% (64/159) on arrival to 26% (65/247) on feed. P. multocida isolation rate from nasal swabs of calves that had no prior treatment for UBRD, regardless of feed medication, increased significantly (Chi-square, P<.01) from 22% (35/139) on arrival to 36% (88/247) on feed. Isolation rates of P. haemolytica and P. multocida, in calves that had previously been treated for respiratory disease, were variable from November 4 to December 2, 1987 (Table 8 & 9). The frequency of isolation of P. haemolytica on arrival (November 4, 1987) in calves who had a rectal temperature greater than 40 degrees C ("sick") was 41%, the same rate in calves without a fever ("healthy"). P. multocida was isolated in 21% of calves with a fever on arrival versus 30% in calves with no fever on arrival.

Antimicrobial sensitivity patterns of P. haemolytica and

P. multocida isolates from calves not previously treated for UBRD were unchanged over time, regardless of feed medication (Table 10-13). Resistance to streptomycin, oxacillin, and lincomycin was evident in the majority of *P. haemolytica* and *P. multocida* isolates.

TABLE 2A. SUMMARY OF TREATMENT FOR UBRD IN 219 CALVES PRIOR TO TRIAL WITH AUREO S-700 AT TERMUENDE RANCH, NOVEMBER 4 - DECEMBER 2, 1987

PARAMETER	AUREO S-700 MEDICATION	CONTROL	TOTAL
# calves	109	110	219
Pre-arrival treatment[a]	25	35	60
- relapses[b]	9	19	28
Treatment on arrival[c]	12	17	29
- 1st pull	9	13	22
- relapse[d]	2	3	5
- relapse[b]	3	4	7
Healthy calves on arrival[e]	75	62	137

a) treatment at the University feedlot, from Oct. 21 - Nov. 3/87

b) reoccurrent treatment at Termuende Ranch in calves initially treated at the University feedlot

c) treatment on arrival at Termuende Ranch, Nov. 4/87

d) reoccurrent treatment in calves initially treated on Nov. 4/87

e) no previous treatment at the feedlot or on arrival at Termuende Ranch (Nov. 4/87). These calves followed on trial.

FIGURE 1:

TREATMENT RATE
in newly arrived calves at the University of Saskatchewan

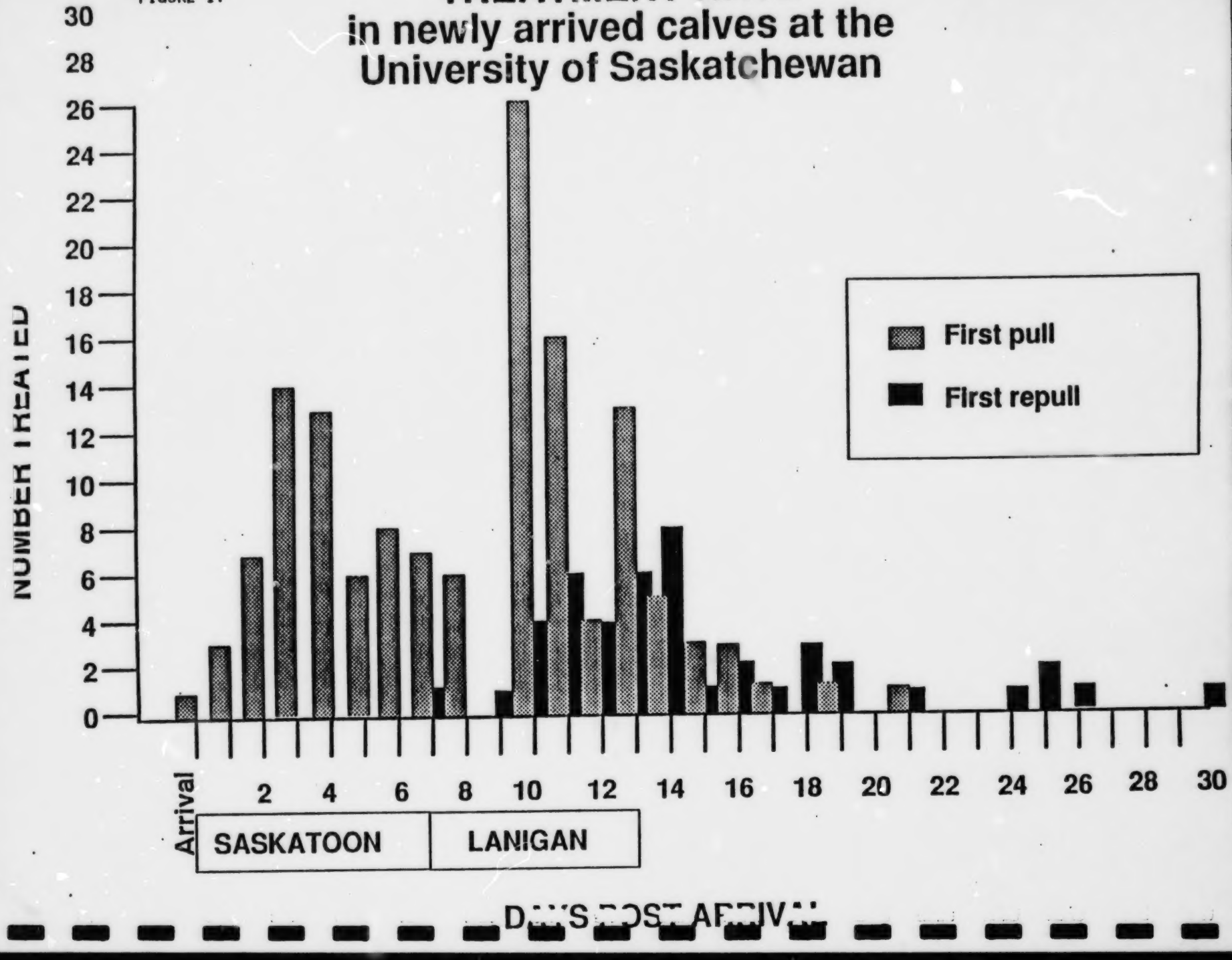

TABLE 2B. SUMMARY OF TREATMENT FOR UBRD IN 137 CALVES ON TRIAL WITH AUREO S-700 AT TERMUENDE RANCH, NOVEMBER 4 - DECEMBER 2, 1987

PARAMETER	AUREO S-700 MEDICATION	CONTROL	TOTAL
Healthy calves on arrival[a]	75	62	137
Treatment on trial[b]	28	31	59
- 1st pull	26	28	54
- relapse	2	3	5
Drug Response on trial[c]	23	28	51
- 1st pull	21	26	47
- relapse	2	2	4
Duration of Treatment[d]	3.6	3.1	3.4
- 1st pull	3.7	3.0	3.3
- relapse	3.0	4.3	3.8
Mortality	1[e]	1[f]	2

a) no previous treatment at feedlot or on arrival (Nov. 4) at Termuende Ranch. These calves followed on Aureo S-700 trial.

b) no. of calves treated for respiratory disease from Nov. 5 to Dec. 2/87, end of trial.

c) Oxytetracycline LP initial drug used. No. of calves that responded to treatment within 48 hrs, by a drop in rectal temperature to below 40 degrees C.

d) length of antimicrobial treatment for UBRD, in days

e) chronic pneumonia and frostbite of feet

f) broken back

FIGURE 2:

TREATMENT RATE
in calves receiving Aureo S-700 in feed (Aureo S-700) vs those without (control)

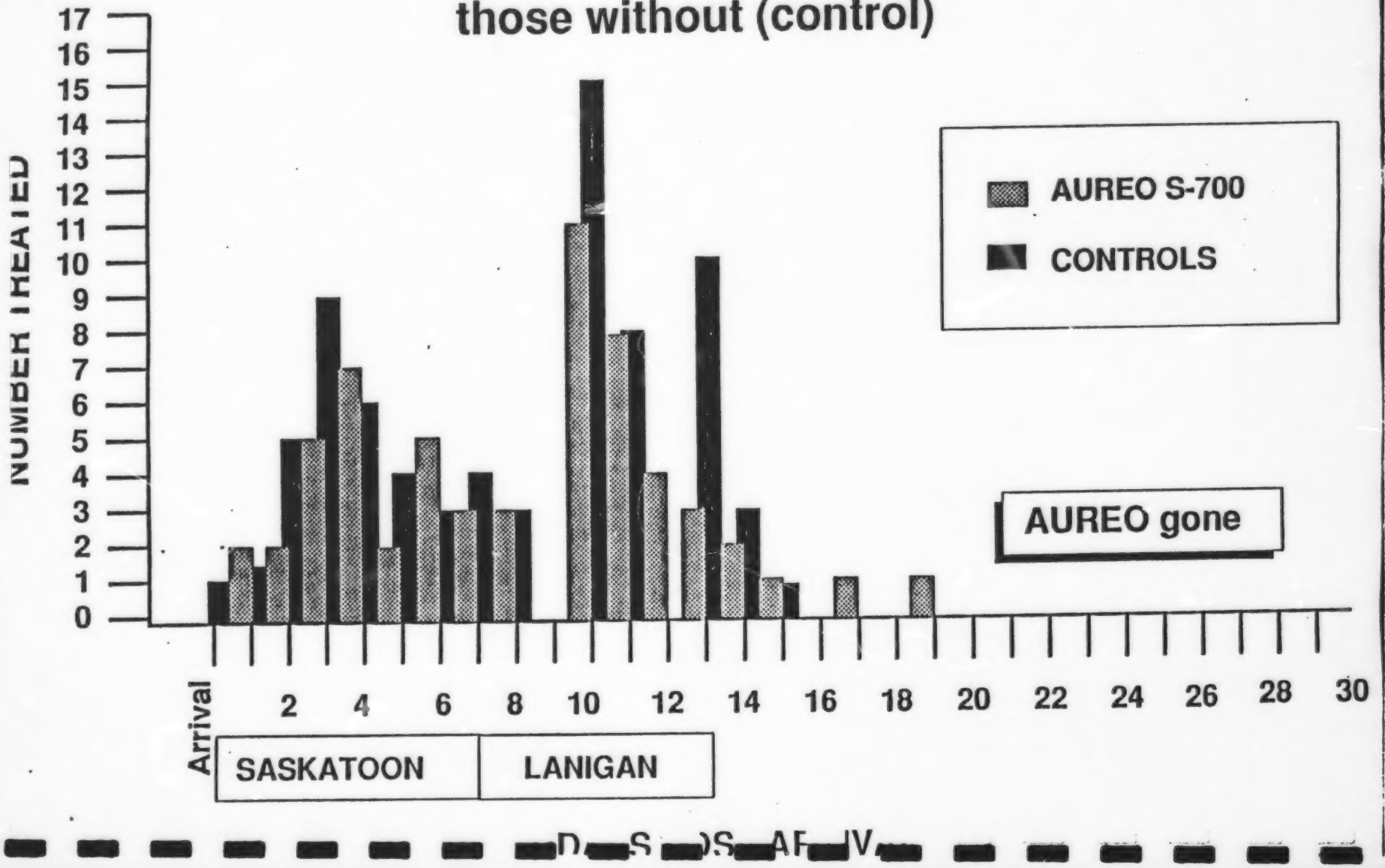

TABLE 3. STUDY OF THE RELATIONSHIP BETWEEN AUREO S-700 FEED MEDICATION AND 1ST TREATMENT FOR UBRD IN 137 CALVES ON TRIAL AT TERMUENDE RANCH, NOV.4 TO DEC. 2, 1987

AUREO S-700 MEDICATION	1ST TREATMENT FOR UBRD YES	NO	TOTAL	TREATMENT RATE, %
YES	26	49	75	35
NO	28	34	62	45
	54	83	137	39

Chi Square Statistic = 2.00 (P>.10)

Since 2.00 is less than 3.84, we can assume that the observed differences are likely due to chance; that is, Aureo S-700 feed medication is not associated with 1st treatment for UBRD.

TABLE 4. STUDY OF THE RELATIONSHIP BETWEEN AUREO S-700 FEED MEDICATION AND REOCCURRENT TREATMENT FOR UBRD IN 137 CALVES ON TRIAL AT TERMUENDE RANCH, NOVEMBER 4 - DECEMBER 2, 1987

	REOCCURRENT TREATMENT			RELAPSE
AUREO S-700 MEDICATION	YES	NO	TOTAL	RATE, %
YES	2	24	26	0.08
NO	3	25	28	0.11
	5	49	54	0.09

Chi Square Statistic = 0.14 (P>.10)

Since 0.14 is less than 3.84, we can assume that the observed differences are likely due to chance; that is, Aureo S-700 feed medication is not associated with reoccurrent treatment for UBRD.

TABLE 5. STUDY OF THE RELATIONSHIP BETWEEN AUREO S-700 FEED MEDICATION AND REOCCURRENT TREATMENT (NOV. 4 - DEC. 2, 1987) FOR UBRD AT TERMUENDE RANCH IN 60 CALVES INITIALLY TREATED AT THE UNIVERSITY FEEDLOT

AUREO S-700 MEDICATION	REOCCURRENT TREATMENT YES	NO	TOTAL	RELAPSE RATE,%
YES	9	16	25	36
NO	19	16	35	54
	28	32	60	47

Chi Square Statistic = 2.01 (P>.10)

Since 2.01 is less than 3.84, we can assume that the observed differences are likely due to chance; that is, Aureo S-700 feed medication is not associated with reoccurrent treatment for UBRD.

TABLE 6. AVERAGE WEIGHT OF CALVES ON A FEED TRIAL WITH AUREO S-700 AT TERMUENDE RANCH, NOVEMBER 4 TO DECEMBER 2, 1987

DATE	PEN 1 - MEDICATED	PEN 2 - CONTROL
NOV. 4/87	250.435	250.861
DEC. 2/87	279.648 +	272.917 +
DEC. 29/87	278.648 +	271.861 +
JAN. 26/88	286.519	285.278
FEB. 23/88	302.491	298.241
MAR. 22/88	333.833 +	325.296 +
APRIL 19/88	340.380	337.75

+ significant difference (Z test, $P<.05$) in weight between calves medicated with Aureo S-700 versus controls.

TABLE 7. MEAN AVERAGE DAILY GAIN (KG/DAY) OF CALVES ON A FEED TRIAL WITH AUREO S-700 AT TERMUENDE RANCH, NOVEMBER 4 TO DECEMBER 2, 1987

DATE	PEN 1 - MEDICATED	PEN 2 - CONTROL
NOV. 4/87		
	1.04 +	0.79 +
DEC. 2/87		
	-0.04	-0.04
DEC.29/87		
	0.28 +	0.48 +
JAN.26/88		
	0.57 +	0.46 +
FEB. 23/88		
	1.12 +	0.97 +
MAR. 22/88		
	0.23 +	0.44 +
APR. 19/88		

+ significant difference (Z test, $P<.05$) in mean average daily gain between calves medicated with Aureo S-700 versus controls

TABLE 8. ISOLATION RATE OF *P. HAEMOLYTICA* IN CALVES PREVIOUSLY TREATED WITH PARENTERAL ANTIMICROBIALS AT VARIOUS TIMES ON TRIAL WITH AUREO S-700

	PEN 1 - MEDICATED		PEN 2 - CONTROL	
	PREVIOUS TREATMENT:		PREVIOUS TREATMENT:	
DATE	YES	NO	YES	NO
NOV. 4[a]	35% (9/26)	40% (33/83)	46% (16/35)	41% (31/76)
NOV. 10[b]	42% (25/60)	29% (14/49)	29% (22/76)	31% (11/35)
NOV. 16[b]	26% (16/62)	21% (10/47)	32% (24/76)	26% (9/35)
DEC. 2[b]	24% (15/63)	22% (10/46)	29% (22/76)	31% (11/35)

a) Arrival at Termuende Ranch. Medication (Aureo S-700) put in feed after isolates collected, at a rate of 700 mg chlortetracycline (CTC) and sulfamethazine (SMZ) per head per day for 7 days (Pen 1).

b) Pen 1 medication reduced to provide 350 mg of CTC and SMZ per head per day.

TABLE 9. ISOLATION RATE OF *P. MULTOCIDA* IN CALVES PREVIOUSLY TREATED WITH PARENTERAL ANTIMICROBIALS AT VARIOUS TIMES ON TRIAL WITH AUREO S-700

	PEN 1 - MEDICATED PREVIOUS TREATMENT:		PEN 2 - CONTROL PREVIOUS TREATMENT:	
DATE	YES	NO	YES	NO
NOV. 4[a]	35% (9/26)	33% (27/83)	46% (14/35)	24% (8/76)
NOV. 10[b]	28% (17/60)	45% (22/49)	26% (20/76)	29% (10/35)
NOV. 16[b]	48% (30/62)	40% (19/47)	45% (34/76)	26% (9/35)
DEC. 2[b]	56% (35/63)	33% (15/46)	39% (30/76)	37% (13/35)

a) Arrival at Termuende Ranch. Aureo S-700 put in feed of Pen 1 after isolates collected, at a rate of 700 mg CTC and SMZ per head per day for 7 days.

b) Pen 1 medication reduced to provide 350 mg of CTC and SMZ per head per day.

TABLE 10. SENSITIVITY PATTERNS OF *P. MULTOCIDA* ISOLATES* TO SELECTED ANTIMICROBIALS AT VARIOUS TIMES ON TRIAL WITH AUREO S-700: PEN 1+

ANTIMICROBIAL	DATE (% sensitive): NOV. 3[a]	NOV. 10[b]	NOV. 16[c]	DEC. 2[d]
Penicillin	100	100	100	100
Tetracycline	100	100	100	100
Streptomycin	87	85	87	73
Neomycin	100	100	100	100
Ampicillin	100	100	100	100
Gentamycin	100	100	100	100
Cephalothin	100	100	100	100
Erythromycin	100	100	100	100
Furadantin	100	100	100	100
Oxacillin	75	69	93	73
Lincomycin	0	0	20	18
Trimethoprim/ Sulfamethoxazole	87	100	100	100

* Kirby-Bauer Test on isolates from calves not previously treated with parenteral antimicrobials

\+ feed medicated with Aureo S-700

a) 8 isolates

b) 13 isolates

c) 15 isolates

d) 11 isolates

TABLE 11. SENSITIVITY PATTERNS OF *P. MULTOCIDA* ISOLATES* TO SELECTED ANTIMICROBIALS AT VARIOUS TIMES ON TRIAL WITH AUREO S-700: PEN 2+

ANTIMICROBIAL	DATE (% sensitive): NOV.3[a]	NOV. 10[b]	NOV. 16[c]	DEC. 2[d]
Penicillin	100	100	100	100
Tetracycline	100	100	100	100
Streptomycin	80	25	60	86
Neomycin	100	100	100	100
Ampicillin	100	100	100	100
Gentamycin	100	100	100	100
Cephalothin	100	100	100	100
Erythromycin	100	100	100	100
Furadantin	100	100	100	100
Oxacillin	60	75	80	86
Lincomycin	0	0	0	0
Trimethoprim/ Sulfamethoxazole	100	100	100	100

* Kirby Bauer Test on isolates from calves not previously treated with antimicrobials

\+ control pen

a) 5 isolates

b) 4 isolates

c) 5 isolates

d) 7 isolates

TABLE 12. SENSITIVITY PATTERNS OF *P. HAEMOLYTICA* ISOLATES* TO SELECTED ANTIMICROBIALS AT VARIOUS TIMES ON TRIAL WI"H AUREO S-700: PEN 1+

ANTIMICROBIAL	DATE (% sensitive): Nov. 3[a]	Nov. 10[b]	Nov. 16[c]	Dec. 2[d]
Penicillin	87	100	100	100
Tetracycline	87	100	100	83
Streptomycin	25	20	17	0
Neomycin	100	100	100	100
Ampicillin	87	100	100	100
Gentamycin	100	100	100	100
Cephalothin	87	100	100	100
Erythromycin	87	80	83	83
Furadantin	100	100	100	100
Oxacillin	25	0	0	0
Lincomycin	0	0	0	0
Trimethoprim/ Sulfamethoxazole	100	100	100	100

* Kirby Bauer Test on isolates from calves not previously treated with parenteral antimicrobials

\+ feed medicated with Aureo S-700

a) 8 isolates

b) 5 isolates

c) 6 isolates

d) 6 isolates

TABLE 13. SENSITIVITY PATTERNS OF *P. HAEMOLYTICA* ISOLATES* TO SELECTED ANTIMICROBIALS AT VARIOUS TIMES ON TRIAL WITH AUREO S-700: PEN 2+

	DATE (% sensitive):			
ANTIMICROBIAL	Nov. 3[a]	Nov. 10[b]	Nov. 16[c]	Dec. 2[d]
Penicillin	100	100	80	33
Tetracycline	100	100	80	33
Streptomycin	0	0	40	0
Neomycin	100	100	100	100
Ampicillin	100	100	80	33
Gentamycin	100	100	100	100
Cephalothin	100	100	100	100
Erythromycin	100	100	100	33
Furadantin	100	100	100	100
Oxacillin	0	0	20	0
Lincomycin	0	0	0	0
Trimethoprim/ Sulfamethoxazole	100	100	100	100

* Kirby Bauer Test on isolates from calves not previously treated with antimicrobials

\+ control pen

a) 4 isolates

b) 2 isolates

c) 5 isolates

d) 3 isolates

DISCUSSION:

In the present study, supplementation in the feed with chlortetracycline and sulfamethazine for the first 28 days on feed in newly arrived calves did not appear to reduce the treatment rate for UBRD nor improve weight gain. The ability of this field trial, however, to identify a true treatment effect is low. Initially 219 calves had been selected, to be fed in at least 2 pens per treatment group. A large majority of these calves became sick prior to the trial and could not be used as study subjects. Space and feeding restrictions at the research ranch limited us to one pen per treatment group. Since our experimental unit was the pen, and we only had one pen per treatment, it was not possible to estimate the within-treatment variability (variance). No meaningful formal statistical evaluation of observed differences was possible (17). In this trial we could not separate a treatment effect from a pen effect (17). The effect of extraneous factors within a pen on measurements is evident by the significant changes in average daily gain in calves within the two pens (Table 7). Similar pen effects could influence any other measurements taken between the medicated and control group.

Numerous experimental trials with CTC and SMZ have been performed over the years, evaluating weight gain and treatment rate in newly arrived calves (18-26). Many of these trials, however, are invalid. They suffer from some of the following design flaws: 1) inadequate sample size, 2) nonrandomization of

subjects to treatment group, 3) incorrect definition of experimental unit, 4) non-blind trial, and 5) poor or absent definitions of disease measured. Average daily gain is often measured only for the first 28 days on trial. As seen in our experiment, a difference was noted the first 28 days but no longer present at 172 days. The initial difference seen may have been a treatment effect, a pen effect or due to chance. Compensatory gain over the feeding period may have reduced any treatment effect initially seen.

Evaluation of isolation rates and sensitivity patterns between the two groups is meaningless because of the flaws in trial design. There appear to be no differences in the two pens, therefore the data was grouped together and studied as one unit, ignoring feed medication.

The nasal isolation rate of P. haemolytica and P. multocida on arrival ranged from 24% to 46%, similar to previous reports (27-30). The frequency of isolation of Pasteurella between calves with a fever ("sick") and those without a fever ("healthy") on arrival was similar, supporting data from Allan (27) and Frank (29), but refuting data from others (13,28,31). P. haemolytica isolation rates decreased over time, in direct conflict with results from Frank (29), but supporting data from Magwood (28). P. multocida isolation rates increased over time, whereas Magwood's data (28) showed a slight reduction in isolation frequency. Stressful conditions may allow the rapid replication of P. haemolytica in the nasal passage, which may explain the higher isolation rate on arrival (29). These calves

had been sorted and handled frequently a few days prior to shipment, allowing time for replication of P. haemolytica. The reason for the increase in frequency of isolation of P. multocida over time is unknown. It is interesting to note that bronchopneumonia associated with P. multocida is more commonly seen in cattle that have been on feed for some time. The value of bacterial isolates from nasal swabs, however, is of little significance, since it has been shown that there is a limited relationship between the microbiology of the upper airways and the microbiology and occurrence of lesions in the bovine lung (27).

Antimicrobial sensitivity patterns were measured using the Kirby-Bauer disk diffusion test. The purpose of examining sensitivity patterns over time was to see if low levels of feed antibiotics would increase antimicrobial resistance in Pasteurella isolates. Based on this data, there was no relationship between feed medication and antimicrobial sensitivity. These results are, however, meaningless, since the number of isolates was too small to show differences, if any existed. The use of the Kirby-Bauer test for antimicrobials when testing animal pathogens may also have been inappropriate since the standards are valid only for human urinary tract pathogens (32). In vitro effectiveness testing of antimicrobials against common respiratory pathogens bears little relationship to the treatment response of UBRD because of the inappropriate tests used to measure sensitivity (30,32), and because there are often marked differences between antimicrobial sensitivities of

isolates from the upper and lower airways of the same animal, those from the lungs having the greater sensitivity (27). The difference seen in drug response rate among the medicated and control pen was not statistically significant. The trend, however, suggested a reduced treatment response in the medicated group, which may have been a result of chance, extraneous factors causing a pen effect, or antimicrobial resistance.

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